

## REMARKS

Applicants have the following comments in support of this amendment and in response to the Office Action of October 25, 2006.

### Claim Amendments – Reference to Disclosure

The claimed pharmaceutical compositions of the present application are directed to formulations of certain new and novel highly-halogenated halogenated xanthenes, including 4,5,6,7-Tetrabromoerythrosin, that the inventors have designed into a chemotherapeutic pharmaceutical composition for chemotherapeutic application.

While Applicants traverse the rejections in the Office Action, in order to advance prosecution of the present applicant, Applicants are amending independent Claims 1, 19, 36 and 37 as outlined below.

Independent Claim 1 has been amended to incorporate the subject matter of former dependent Claim 2, which has been canceled without prejudice or disclaimer. Specifically, amended independent Claim 1 is directed to an *injectable composition* consisting of a halogenated xanthene at a concentration of greater than about 0.001% to less than about 20% that is designed for chemotherapeutic treatment of diseases of *human tissue*.

Independent Claim 19 has been amended such that it is directed to a chemotherapeutic pharmaceutical composition designed for intracorporeal administration *to humans*. Administration to humans is clearly disclosed throughout the specification of the present application, including in the Abstract. Independent Claims 36 and 37 have been similarly amended.

Accordingly, Applicants respectfully submit that the amendments to Claims 1, 19, 36 and 37 are not adding any new matter and are clearly supported by the application as filed. Therefore, it is requested that they be entered and considered at this time.

Novel Composition of Matter

Amended independent Claims 1, 19, 36 and 37 are directed to various pharmaceutical compositions that contain new and novel, highly-halogenated halogenated xanthenes (i.e., 4,5,6,7-Tetrabromoerythrosin, Monobromoerythrosin, Dibromoerythrosin, Tribromoerythrosin, Monochloro-erythrosin, Dichloroerythrosin and Trichloroerythrosin), none of which are believed to have been described or suggested in the prior art, including that art cited by the Examiner in this or any of the prior actions for this application. As explained below, the compounds are not obvious extensions of those compounds previously known.

More specifically, due to the relative complexity of synthesis of these new compounds posed by steric hindrance<sup>1</sup> from the dense content of halogens, along with other factors such as photochemical instability that make such compounds relatively difficult to produce and handle, Applicants submit that they are the first to invent the claimed new compounds which represent a novel extension to the halogenated xanthene family. For example, Rose Bengal (a very stable molecule which formerly comprised the most halogen-rich member of the halogenated xanthene family) has been known for over 100 years. Nonetheless, knowledge of its properties and those of

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<sup>1</sup> Steric hindrance is spatial interference inhibiting or preventing the close arrangement of adjacent atoms within a molecule due to the sizes of the overlapping electron clouds of the adjacent atoms, and poses particularly difficult synthetic challenges when large atoms, such as chlorine, bromine and iodine, are incorporated into a molecule.

the other previously known halogenated xanthenes (such as phloxine B, erythrosin, and eosin) has not led those skilled in the art (prior to Applicants' conception) to conceive, suggest, synthesize or investigate the claimed highly-halogenated halogenated xanthenes. Nor has anyone else conceived of pharmaceutical compositions consisting of halogenated xanthenes for any chemotherapeutic treatment prior to Applicants' work.

Applicants conceived of these new compounds in an effort to improve chemotherapeutic treatment of diseases of human tissue, the performance of which may be enhanced by increasing the halogen density of the halogenated xanthene molecules, for example by including greater numbers of halogen atoms or increasing their atomic number. A consequence of such enrichment is greatly reduced stability of the xanthene molecule, especially upon exposure to optical radiation. Such trends in synthetic complexity and instability run counter to the teachings of the prior art (such as that of Heitz et al., as cited by the Examiner in the present Office Action) which are predicated on use of relatively stable, inexpensive molecules that are added to livestock feed. Since such animals are unlikely to be fed in the dark, investigators such as Heitz presumably would not consider developing or using photochemically unstable analogs of the halogenated xanthenes, nor would they likely select new analogs requiring complex (and presumably relatively expensive) synthesis. Hence, such investigators were not motivated to consider or investigate, and there is no evidence that they conceived of or considered, such novel compounds since these compounds would have no obvious relevance for the uses employed by such investigators.

Accordingly, Applicants respectfully submit that the claimed highly-halogenated halogenated xanthenes, and the various claimed pharmaceutical compositions containing such highly-halogenated halogenated xanthenes, of the claims of the present application are novel over the prior art.

Applicants appreciate the Examiner's withdrawal of many of the prior objections and rejections.

Applicants will now address each of the Examiner's remaining objections and rejections in the order in which they appear in the Office Action.

#### Objection To Prior Amendment - Status of Claims 28-35

In the Office Action, the Examiner objects to the prior amendment as not providing the status of Claims 28-35.

Claims 28-35 have previously been canceled. Accordingly, Applicants are listing Claims 28-35 herein as "canceled." This should overcome the Examiner's objection.

#### Claim Rejections – 35 USC §102

##### Heitz et al.

In the Office Action, the Examiner issues a new rejection and rejects Claims 1, 9-11, 19, and 27 under 35 USC §102(b) as being anticipated by Heitz et al. (USP 4,846,789). This rejection is respectfully traversed.

In particular, and contrary to the Examiner's contentions, Heitz simply does not disclose or suggest the novel, highly-halogenated halogenated xanthenes recited in independent Claims 1, 19, 36 and 37, nor the pharmaceutical compositions of which they are a part.

The Examiner, however, appears to be contending that the known halogenated xanthene dyes in Heitz can be manipulated to arrive at the claimed halogenated xanthenes and that the vague disclosure in Heitz encompasses the claimed compounds. Such a rejection is improper under the

patent rules. Further, such hypothetical manipulation and modifications are not an anticipation of the claimed compositions.

For example, it cannot be disputed that Heitz does not expressly disclose the claimed compound 4,5,6,7-Tetrabromoerythrosin. The Examiner cites Heitz as disclosing a formulation comprising derivatives of fluorescein and these derivatives may have one or more substitutes in the 4, 5, 6, 7, 2', 4', 5' and 7' positions selected from the group consisting of fluoro, chloro, bromo, iodo, and etc. The Examiner then contends that this formulation encompasses the recited compounds such as 4,5,6,7-Tetrabromoerythrosin. This is improper.

MPEP §2132.02 states that:

**"A GENERIC CHEMICAL FORMULA WILL ANTICIPATE A CLAIMED SPECIES COVERED BY THE FORMULA WHEN THE SPECIES CAN BE "AT ONCE ENVISAGED" FROM THE FORMULA**

When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated. *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962)."

In the present case, Heitz discloses at col. 4, lines 21-26, which is relied upon by the Examiner in the Office Action, "[t]he derivatives of fluorescein (C.I. No. 45350) having one or more substituents in the 4, 5, 6, 7, 2', 4', 5' and 7' positions selected from the group consisting of F, Cl, Br, I, --NO<sub>2</sub>, --COOH and --OH are especially important." Hence, it appears that Heitz is discussing the

possibility of substitution at one or more of 8 positions with one of 7 different elements/compounds. This is hardly the limited class discussed in MPEP 2131.02. In fact, it is believed that there are over 5 million possible combinations in this disclosure in Heitz. This is clearly not the situation where one skilled in the art could at once envisage the claimed compounds of the present application. Only through the use of hindsight reconstruction using the claimed compounds as a blue print or endless experimentation could one skilled in the art arrive at the claimed compound from this disclosure in Heitz. Therefore, in accordance with MPEP 2131.02, Heitz cannot be said to anticipate the claimed compound, and this rejection should be withdrawn.

Further, as explained *supra*, the claimed compositions are novel and nonobvious. In addition, as explained *supra* and below, one of ordinary skill in the art would not have made the Examiner's manipulation and modifications of the halogenated dyes to arrive at the claimed invention, and there is no motivation for one of ordinary skill in the art to make such modifications. Accordingly, since Heitz fails to teach or suggest the existence of the claimed halogenated xanthenes (such as 4, 5, 6, 7-Tetrabromoerythrosin), Heitz cannot anticipate nor render obvious the claimed invention.

More specifically, Heitz is concerned with certain optical properties of *known* halogenated xanthenes, and thus provides no motivation for conceptualization or investigation of the highly-halogenated molecules of independent Claims 1, 19, 36 and 37.

Furthermore, Heitz does not disclose or suggest the presently claimed therapeutic compositions or chemotherapeutic treatments. Instead of teachings directed to pharmaceutical compositions for treatment of diseases of human tissue (as is the subject of Applicants' claimed invention), Heitz is directed to *pesticidal compositions and their uses in livestock* (i.e., *ex vivo* killing

of intestinal parasites to prevent infection, wherein the pathogenic organisms are killed by exposure to light outside of the infected animal before they can infect another animal).

Accordingly, the disclosure in Heitz does not therapeutically affect the animal to which the photosensitive dye is fed, but rather serves to break the chain of transmission of pathogens from one infected animal to another once the pathogens are exposed to light outside of the host animal's body. Therefore, the disclosure in Heitz is not directed to nor does it disclose or suggest an injectable chemotherapeutic composition for human use (as required in Claims 1, 36 and 37 of the present application); nor does it comprise use of a dye in the preparation of an intracorporeal chemotherapeutic medicament for human use (as required in Claim 19). The subject matter of Heitz is so far removed from the subject matter of the claimed invention, that one skilled in the art would not be motivated in any way to rely or refer to this reference for compositions for treatment of diseases of human tissue, as in the claimed invention.

Further, Heitz does not disclose or suggest a chemotherapeutic pharmaceutical composition in any form, as required in independent Claims 1, 19, 36 and 37. Instead, Heitz discloses use of light energy to activate a photosensitizer in order to kill intestinal parasites that have taken up a portion of the photosensitizer. This pesticidal action doesn't even occur within the host animal, but instead is purported to occur upon exposure of excreted fecal material to ambient light.

As discussed *supra*, since the disclosure of Heitz is directed to feed additives for livestock, such additives presumably must exhibit several features, including low cost and good stability under typical conditions of agricultural use and storage. As noted by Applicants *supra*, the highly-halogenated xanthenes are unlikely to meet these objectives, since they require complex synthesis and are photochemically labile.

Furthermore, the recitation by Heitz cited by the Examiner on p. 4 of the Office Action, allegedly showing that *all derivatives* of fluorescein having "one or more substitutes in the 4, 5, 6, 7, 2', 4', 5' and 7' positions selected from the group consisting of fluoro, chloro, bromo, iodo" are thereby disclosed by Heitz, represents an improper generalization of such disclosure. What Heitz actually states is the following:

"The xanthene derivatives, and especially the xanthene dyes having colour index numbers of 45000-45999, are present preferred in practicing the invention. The xanthene dyes are disclosed on Pages 4417-4430 of the aforementioned publication entitled Colour Index, and reference may be had thereto for numerous specific xanthene dyes. Additional xanthene dyes include those prior art derivatives of xanthene per se which absorb electromagnetic radiation having wave lengths falling within the ranges set out above. The derivatives of fluorescein (C.I. No. 45350) having one or more substituents in the 4, 5, 6, 7, 2', 4', 5' and 7' positions selected from the group consisting of F, Cl, Br, I, --NO<sub>2</sub>, --COOH and --OH are especially important...." (col. 4, lns. 12-27)

Thus, Heitz states in the first sentence that dyes having certain Colour Index numbers are preferred for the invention, while the second sentence states that dyes on pp. 4417-4430 of the Colour Index are incorporated into the invention. Heitz then states in the third sentence that *known prior art derivatives* are incorporated into the invention. In the fourth sentence, Heitz states that derivatives of fluorescein having one or more substituents are especially important. Clearly, Heitz does not disclose specific compounds such as those presently claimed by Applicants, and more importantly it is clear that this disclosure concerns only *known compounds* described in the Colour Index.<sup>2</sup> Hence, there is no disclosure of the specific compounds claimed in the present application. Further, as explained *supra*, the Examiner's use of the generalized formula is improper under the patent rules.

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<sup>2</sup> A copy of the pages, cited in Heitz, of the Colour Index is provided with this paper.

Even if taken literally, Applicants still traverse the Examiner's interpretation of this passage from Heitz. In the passage cited by the Examiner, Heitz states, "derivatives of fluorescein ... having one or more substituents ... are especially important." Does "one or more substituents" disclose Applicants' novel compositions of matter claimed in independent Claims 1, 19, 36 and 37? The following table sets forth the substituents in Applicants' claimed novel compositions of matter:

| Compound                     | Substituents at 4, 5, 6, 7 positions | Substituents at 2', 4', 5', 7' positions | Total number of substituents |
|------------------------------|--------------------------------------|--|------------------------------|
| 4,5,6,7-Tetrabromoerythrosin | 4 bromine atoms                      | 4 iodine atoms                           | 8                            |
| Monobromoerythrosin          | 1 bromine atom                       | 4 iodine atoms                           | 5                            |
| Dibromoerythrosin            | 2 bromine atoms                      | 4 iodine atoms                           | 6                            |
| Tribromoerythrosin           | 3 bromine atoms                      | 4 iodine atoms                           | 7                            |
| Monochloroerythrosin         | 1 chlorine atom                      | 4 iodine atoms                           | 5                            |
| Dichloroerythrosin           | 2 chlorine atoms                     | 4 iodine atoms                           | 6                            |
| Trichloroerythrosin          | 3 chlorine atoms                     | 4 iodine atoms                           | 7                            |

Thus, the disclosure of "one or more" substituents at positions 4, 5, 6, 7, 2', 4', 5' and 7' is quite a stretch from the 5-8 substituents present in Applicants' high-halogenated halogenated xanthenes. Accordingly, the Examiner has clearly overextended the breadth of the disclosure of Heitz, and as explained supra, such an overextension is improper.

Since Heitz fails to teach or suggest the claimed halogenated xanthenes or the claimed pharmaceutical compositions, Heitz cannot anticipate nor render obvious the claimed invention of the present application. Moreover, one of ordinary skill in the art would not be motivated by Heitz to extend the disclosure of Heitz to create Applicants' novel high-halogenated halogenated xanthenes

and then incorporate them into completely unrelated products. Further, the extension of the disclosure of Heitz to arrive at the claimed invention is improper.

For at least the above-stated reasons, Heitz fails to disclose or suggest the pharmaceutical compositions of the independent claims of the present application, and the rejection of these claims over Heitz is improper. Accordingly, the claims of the present application are patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

Claim Rejections – 35 USC §103

Heitz et al.

The Examiner also rejects Claims 1-2, 9-11, 19, 27, 36 and 37 under 35 USC §103(a) as being unpatentable over Heitz. This rejection is also respectfully traversed.

First, as explained *supra* with regard to the §102 rejection, Heitz does not disclose or suggest the novel, highly-halogenated halogenated xanthenes recited in independent Claims 1, 19, 36 and 37. Since Heitz fails to teach or suggest the existence of these halogenated xanthenes (such as 4, 5, 6, 7-Tetrabromoerythrosin), Heitz cannot render obvious the claimed invention.

Second, as explained *supra*, the Examiner's extension of the disclosure of the formulation in Heitz to encompass the claimed invention is improper under Patent Office rules.

Third, also as explained *supra* with regard to the §102 rejection, Heitz does not disclose or suggest the novel chemotherapeutic compositions recited in independent Claims 1, 19, 36 and 37. Since Heitz fails to teach or suggest the existence of such compositions (such as the injectable medicaments of independent Claims 1, 36 and 37), Heitz cannot render obvious the claimed invention.

Fourth, the Examiner alleges that the claimed compositions differ from those of Heitz solely in certain result effective variables such as concentration. However, Applicants' invention is not obvious since it is not predicated on optimizing concentration for a photodynamic process (such as the process utilized by Heitz) but rather the fundamental discovery that at certain concentrations and administration means a completely new and unexpected process occurs (i.e., chemotherapeutic activity). Such activity is novel in light of all known prior art, and especially that of Heitz.

In particular, Heitz is predicated on photodynamic activation of a dye taken up by pathogens in the gut of livestock that have been fed such dye as a food additive. This is clearly described in the following passage:

"When the host animal is fed the dye described herein, the dye is admixed with the food to be digested and passes through the gastrointestinal tract. The dye is in contact with the exposed skin of the immature larvae stages and adult stages residing in the gastrointestinal tract, and it is also present in the food consumed by the adult nematodes. As a result, the nematodes in the immature larvae stages and/or adult stage appear to ingest, assimilate, absorb or otherwise incorporate the dye into their tissues.... The feces contain substantially all of the administered dye that is not incorporated in the larvae and adult nematodes residing in the gastrointestinal tract or in the eggs. The fecal pats are normally exposed to visible light, and the hatching eggs and larvae stages developing therefrom are likewise exposed to visible light at some stage of their development. The large amounts of dye present initially in the eggs and incorporated in the developing larvae feeding in the dye containing fecal pat result in one or more lethal oxidative reactions when exposed to visible light.... In the presence of visible light, substantially all of the larvae are killed before they are able to reinfect the animal host." (Heitz, col. 5, ln. 62 – col. 6, ln. 20)

Thus, Heitz teaches that the dye is inert in the livestock ("the feces contain substantially all of the administered dye that is not incorporated in the [pathogens]" -- thus the dye passes through the animal unchanged) and that it functions within the excreted pathogens upon subsequent exposure of the pathogens to ambient light. This is in no manner a disclosure of a chemotherapeutic activity

or a chemotherapeutic composition, as claimed in the present application. Moreover, one of skill in the art would not be led by this disclosure to discover the mechanisms, concentrations, formulations and uses of the claimed invention.

For at least the above-stated reasons, Heitz fails to disclose or suggest the pharmaceutical compositions and medicaments of the present application, the rejection is improper, and the optimum or workable range would not result from routine experimentation. Accordingly, the claims of the present application are clearly patentable over the cited reference, and it is respectfully requested that this rejection be withdrawn.

#### Double Patenting

The Examiner also provisionally rejects Claims 1-2, 9-11, 19, 27, 36 and 37 on the grounds of nonstatutory obvious-type double patenting as being unpatentable over copending Application No. 09/799,795 [sic 09/799,785]. This rejection is also respectfully traversed.

While Applicants traverse this rejection, in order to advance the prosecution of this application, Applicants are filing herewith a terminal disclaimer over the '785 application and fee and submit that such action overcomes the Examiner's provisional rejection.

Accordingly, it is respectfully requested that this provisional rejection be withdrawn.

Interview Request

If the Examiner still wishes to reject the claims of the present application after considering this amendment, then Applicants request an interview with the Examiner to discuss the rejections in further depth. In such a case, it is respectfully requested that the Examiner contact the undersigned to set-up such an interview prior to the issuance of a further Office Action for this application.

Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable condition and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any further fee should be due for this amendment, extension of time, or terminal disclaimer, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

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/Mark J. Murphy/  
Mark J. Murphy  
Registration No. 34,225

COOK, ALEX, McFARRON, MANZO,  
CUMMINGS & MEHLER, Ltd.  
200 West Adams Street, Suite 2850  
Chicago, Illinois 60606  
(312) 236-8500

Customer No. 26568